AMENDMENTS TO THE DRAWINGS

Please replace the Figures 12, 24 and 25 with the corresponding Replacement Sheets provided herewith.

REMARKS

Claims 32-34, 36, and 39-82 are currently pending in the Application. Applicants note with appreciation that the previous rejections over Bagwell or Nazarenko in view of applied secondary references have been withdrawn.

The Examiner has raised a number of objections and rejections. For clarity, these objections and rejections are listed below in the order in which they will be addressed:

1. The application allegedly fails to comply with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures;
2. Claims 32 and 57 and the claims dependent therefrom are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite;
3. Claims 32, 33, 39, 48-50, 51, 52, 54, 55, 58, 60, 62, 63, 72-76, 78, 79, 81, and 82 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,215,899 to Dattagupta, *et al.*, (hereinafter "Dattagupta") in view of Lau, *et al.*, Science 294:858-862 (2001)(hereinafter "Lau");
4. Claims 34 and 61 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Lau, in further view of U.S. Patent No. 5,985,557 to Prudent, *et al.*, (hereinafter "Prudent");
5. Claims 36, 44-47, 59, and 68-71 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Morris, *et al.*, J. Clin. Microbiol., 1996 Dec., 34(12):2933-6, (hereinafter "Morris");
6. Claims 40-43, 53, 64-67, and 77 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Marras, *et al.*, Genet Anal. 1999 Feb., 14(5-6):151-6 (hereinafter "Marras");
7. Claims 56 and 80 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Lau, in further view of U.S. Patent No. 5,985, 563 to Hyidig-Nielsin, *et al.*, (hereinafter "Hyidig-Nielsin").

OBJECTIONS

1. The Examiner alleges that the application fails to comply with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence

Disclosures. In particular, the Examiner asserts that Figures 12, 24, and 25 comprise sequences that do not have sequence identifiers.

Applicants herein amend the specification to include brief descriptions of the sequence identifiers for the nucleic acid sequences shown in Figures 24 and 25. The brief description of Figure 12 was previously amended to contain these descriptions. In addition, Applicants provide herewith Replacement Sheets for drawing 12, 24, and 25, amended to show sequence identifiers for the depicted nucleic acids. The only changes in these drawings are the addition of the sequence identifiers and these amendments do not contain new matter.

Applicants have also amended the specification to include a substitute "Sequence Listing" pursuant to 37 C.F.R. §§ 1.821-1.825. Applicants submit a substitute Sequence Listing in paper copy and computer readable form, along with a Certificate stating that the computer readable form and the paper copy of the Sequence Listing are identical. The amendments to the Sequence Listing do not contain new matter.

Applicants submit that the application complies with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures and respectfully request that these objections be removed.

REJECTIONS

The Claims Are Not Indefinite

2. Claims 32 and 57 and the claims dependent therefrom are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. In particular, the Examiner asserts that the phrase "wherein said second region can form a hairpin loop when said probe is hybridized" in unclear as to whether the limitations set forth are part of the claimed invention. Applicants respectfully disagree for the reasons provided in the Amendment and Response filed on March 20, 2006. Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Applicants herein amend Claims 32 and 57 to recite "wherein said first portion and said second portion hybridize to each other when said unlabeled probe is hybridized to said microRNA." Applicants

submit that Claims 32 and 57 as amended are not indefinite and respectfully request that this rejection be removed.

The Claims Are Not Obvious

Prima facie obviousness requires: 1) a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings; 2) the prior art must teach of a reasonable expectation of success should the suggested combination or modification take place; and 3) the prior art must teach or suggest all the claim limitations. M.P.E.P § 2143. A showing of obviousness will fail if any one of these elements is not met. As explained in more detail below, none of the cited combinations of references cited sets forth each and every element of the rejected claims.

3. Claims 32, 33, 39, 48-50, 51, 52, 54, 55, 58, 60, 62, 63, 72-76, 78, 79, 81, and 82 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,215,899 to Dattagupta in view of Lau (Office Action page 5). Claims 33, 39, 48-50, 51, 52, 54, and 55 depend from Claim 32 and incorporate each recited element of Claim 32. Claims 58, 60, 62, 63, 72-76, 78, 79, 81, and 82 depend from Claim 57 and incorporate each recited element of Claim 57. Claims 32 and 57 as amended recite the step of disassociating the microRNA and the unlabeled probe. Support for this amendment is found, *e.g.*, in the paragraph that bridges pages 30 and 31, and particularly at page 31, line 3. As recited in Claims 32 and 57, the unlabeled probe comprises a first region that is complementary to said microRNA and a second region that is not complementary to said microRNA, wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion hybridize to each other when said unlabeled probe is hybridized to said microRNA.

As the Examiner has noted, Dattagupta does not disclose microRNA detection (Office Action page 5). Dattagupta is directed toward detection of nucleic acids by ligating a probe to a target nucleic acid (see, *e.g.*, Dattagupta at: Title on page 1; page 3 at lines 22-24; Example 1 starting on page 9 at line 33; Claim 1; and Figure 4). Dattagupta does not teach or suggest a method comprising the step of disassociating the target from

the unlabeled probe. Rather, Dattagupta creates complex in which the probe is covalently linked to the target nucleic acid.

Lacking teachings of either microRNA detection, or of a method comprising a step of disassociating a microRNA from the unlabeled probe, Dattagupta clearly does not disclose a method for analyzing microRNAs comprising formation of an RNA detection structure comprising a microRNA and an unlabeled probe having the features recited in the instant claims, disassociation of the microRNA from the unlabeled probe, and detection of the formation of the RNA detection structure.

Lau fails to cure this deficiency. Lau teaches the observation of microRNAs in *C. elegans*. However, Lau fails to teach the use of unlabeled probes in the detection of microRNA, or a method comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe having the features recited in the instant claims, and further comprising the step of disassociating the microRNA from the unlabeled probe. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Dattagupta and Lau does not teach or suggest all the limitations of Claims 32, 33, 39, 48-50, 51, 52, 54, 55, 58, 60, 62, 63, 72-76, 78, 79, 81, and 82, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

4. Claims 34 and 61 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Lau, in further view of Prudent (Office Action page 7). Claim 34 depends from Claim 32 and incorporates each recited element of Claim 32. Similarly, Claim 61 depends from Claim 57 and incorporates each recited element of Claim 57. Claims 32 and 57 as amended recite a method comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe and further comprising the step of disassociating the microRNA from the unlabeled probe. As recited in Claims 32 and 57, the unlabeled probe comprises a first region that is complementary to said microRNA and a second region that is not complementary to said microRNA, wherein a first portion of said second region is complementary to a

second portion of said second region, wherein said first portion and said second portion hybridize to each other when said unlabeled probe is hybridized to said microRNA.

The deficiencies of Dattagupta and Lau are described above. The further combination with Prudent fails to cure these deficiencies. Prudent does not teach a method comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe having the features recited herein, wherein the method further comprises the step of disassociating the microRNA from the unlabeled probe.

While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Dattagupta, Lau, and Prudent does not teach or suggest all the limitations of Claims 34 or Claim 61, and the combination therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

5. Claims 36, 44-47, 59, and 68-71 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Morris. Each of claims 36, 44-47, 59, and 68-71 depend from either Claim 32 or Claim 57. Claims 32 and 57 as amended recite a method comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe and further comprising the step of disassociating the microRNA from the unlabeled probe. As recited in Claims 32 and 57, the unlabeled probe comprises a first region that is complementary to said microRNA and a second region that is not complementary to said microRNA, wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion hybridize to each other when said unlabeled probe is hybridized to said microRNA.

The deficiencies of Dattagupta are described above. Morris does not cure these deficiencies. Morris describes the detection of HCV RNA using the "TaqMan" fluorogenic method. Morris does not teach a method comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe having the features recited herein, the method further comprising the step of disassociating the target from the unlabeled probe.

While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Dattagupta and Morris does not teach or suggest all the limitations of Claims 36, 44-47. 59, and 68-71, and the combination therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

6. Claims 40-43, 53, 64-67, and 77 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Marras.

Each of claims 40-43, 53, 64-67, and 77 depend from either Claim 32 or Claim 57. Claims 32 and 57 as amended recite a method comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe and further comprising the step of disassociating the microRNA from the unlabeled probe. As recited in Claims 32 and 57, the unlabeled probe comprises a first region that is complementary to said microRNA and a second region that is not complementary to said microRNA, wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion hybridize to each other when said unlabeled probe is hybridized to said microRNA.

The deficiencies of Dattagupta are described above. The combination with Marras does not cure these deficiencies. Marras teaches the use of labeled "molecular beacon" probes for detection of nucleic acids. Marras does not teach a method for analyzing microRNAs comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe having the features recited herein, the method further comprising the step of disassociating the target from the unlabeled probe.

While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Dattagupta and Marras does not teach or suggest all the limitations of Claims 40-43, 53, 64-67, and 77, and the combination therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

7. Claims 56 and 80 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dattagupta in view of Lau, in further view of Hyidig-Nielsin (Office

Action page 11-12). Claim 56 depends from Claim 32 and incorporates each recited element of Claim 32. Similarly, Claim 80 depends from Claim 57 and incorporates each recited element of Claim 57. Claims 32 and 57 as amended recite a method comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe and further comprising the step of disassociating the microRNA from the unlabeled probe. As recited in Claims 32 and 57, the unlabeled probe comprises a first region that is complementary to said microRNA and a second region that is not complementary to said microRNA, wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion hybridize to each other when said unlabeled probe is hybridized to said microRNA.

The deficiencies of Dattgupta and Lau are described above. The further combination with Hyidig-Nielsin fails to cure these deficiencies. Hyidig-Nielsin teaches methods of detecting sexually transmitted diseases using PNA probes. Hyidig-Nielsin does not does not teach a method for analyzing microRNAs comprising the formation of an RNA detection structure comprising a microRNA and an unlabeled probe having the features recited herein, the method further comprising the step of disassociating the target from the unlabeled probe.

While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Dattagupta, Lau, and Hyidig-Nielsin does not teach or suggest all the limitations of Claims 56 and 80, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all objections and rejections have been addressed and should be removed, and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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